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10/551,565	02/08/2006	Edward L.G. Pryzdial	701826-57320	4718

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,565	PRYZDIAL, EDWARD L.G.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/20/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-10,12-19 and 24* is/are pending in the application.

4a) Of the above claim(s) *2,7-9,12,13,18,19 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,10 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/20/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-4, 7-10, 12-19 and 24 are pending. Claims 2, 7-9, 12, 13, 18, 19 and 24 are withdrawn for pertaining to a non-elected invention or species, elected without traverse in the response filed 04/17/2008. The elected invention is Group IV, drawn to a method of accelerating blood clot dissolution comprising administering Factor Xaγ or a pharmaceutical composition comprising Factor Xaγ, and the elected species condition is thrombosis, the fibrolytic agent is tissue plasminogen activator, and the thrombin inhibitor is heparin. Prior art was found on each of these elected species and therefore the search was not extended in accordance with MPEP § 803.02.

Withdrawn Claim Objection

2. The objection to claim 4 is withdrawn in light of the arguments on page 5 filed 11/20/2008.

Withdrawn Claim Rejections - 35 USC § 102

3. The rejection of claims 20-23 under 35 U.S.C. 102(b) as being anticipated by Grundy *et al.* (*Biochem.*, **2001**, *40*, 6293-6302, citation 1 on the Information Disclosure Statement filed 11/28/2007) is moot because the claims were cancelled in the response filed 11/20/2008.

Maintained Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Review of Previously Issued Rejections

5. Claims 1, 3, 4, 10, 14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grundy *et al.* (*Biochem.*, **2001**, *40*, 6293-6302, citation 1 on the Information Disclosure Statement filed 11/28/2007) in view of Gladstone *et al.* (*CNAJ*, **2001**, *165*, 311-7). The rejection as it pertains to claims 5, 6, and 11 is moot because these claims were cancelled in the response filed 11/20/2008.

6. Claim 1 is drawn to a method of accelerating blood clot dissolution in a subject in need thereof by administering Factor Xaγ coagulation protein comprising a basic C-terminal amino acid in an amount effective to dissolve said blood clot.

7. The claim term "Factor Xaγ coagulation protein" is defined on page 7, lines 1-7 of the instant specification as follows: Factor Xa bound to procoagulant phospholipid (proPL) and cleaved by plasmin (PN) yields three fragments with molecular weights of 33, 13 and 3 kD which are collectively referred to as Factor Xaγ. The specification states that the presence of proPL during cleavage is critical for the formation of Factor Xaγ.

8. Grundy *et al.* teach that PN cleavage of Factor Xa under phospholipid binding conditions yields three fragments, two of which are 33 and 13 kD (Figure 1). Grundy *et al.* also teach that these fragments have exposed C-terminal lysine residues, that they play a role in fibrinolysis (or blood clot dissolution) and that they accelerate tissue plasminogen activator (t-PA) resulting in

enhanced plasmin generation (p. 6294, col. 1). Grundy *et al.* teach compositions comprising these fragments, Factor Xaγ33/13 (p. 6294, col. 1).

9. Grundy *et al.* do not explicitly state that these compositions are used in a method for accelerating blood clot dissolution.

10. Gladstone *et al.* teach that t-Pa administration can be used to treat stroke thrombosis.

11. It would have been obvious to the skilled artisan to administer the Factor Xaγ taught by Grundy *et al.* to subjects having thrombosis. The skilled artisan would have been motivated to do so in light of the teaching of Gladstone *et al.* that t-Pa can be used to treat thrombosis and the teaching of Grundy *et al.* that Factor Xaγ accelerates t-Pa. There would have been a reasonable expectation of success given that Grundy *et al.* teach that Factor Xaγ leads to enhanced plasmin generation. The combined teaching of Grundy *et al.* and Gladstone satisfies all of the limitations of claims 1, 3, and 10. With respect to claim 4, it would be obvious to administer the Factor Xaγ prophylactically because it is obvious to use Factor Xaγ therapeutically. With respect to claim 14, it would have been further obvious to administer both t-Pa and Factor Xaγ given that they both contribute to the fibrinolysis process. With respect to claim 17, it is obvious to optimize the mode of administration through routine experimentation.

12. Claims 1, 3, 4 10, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grundy *et al.* (*Biochem.*, **2001**, *40*, 6293-6302, citation 1 on the Information Disclosure Statement filed 11/28/2007) in view of Llevadot *et al.* (*JAMA*, **2001**, *286*, 442-9). The rejection of claims 5, 6 and 11 is moot because these claims were cancelled in the response filed 11/20/2008.

13. Claim 1 is drawn to a method of accelerating blood clot dissolution in a subject in need thereof by administering Factor Xaγ coagulation protein comprising a basic C-terminal amino acid in an amount effective to dissolve said blood clot.

14. The claim term "Factor Xaγ coagulation protein" is defined on page 7, lines 1-7 of the instant specification as follows: Factor Xa bound to procoagulant phospholipid (proPL) and cleaved by plasmin (PN) yields three fragments with molecular weights of 33, 13 and 3 kD which are collectively referred to as Factor Xaγ. The specification states that the presence of proPL during cleavage is critical for the formation of Factor Xaγ.

15. Grundy *et al.* teach that PN cleavage of Factor Xa under phospholipid binding conditions yields three fragments, two of which are 33 and 13 kD (Figure 1). Grundy *et al.* also teach that these fragments have exposed C-terminal lysine residues, that they play a role in fibrinolysis (or blood clot dissolution) and that they accelerate tissue plasminogen activator (t-PA) resulting in enhanced plasmin generation (p. 6294, col. 1). Grundy *et al.* teach compositions comprising these fragments, Factor Xaγ33/13 (p. 6294, col. 1).

16. Grundy *et al.* do not explicitly state that these compositions are used in a method for accelerating blood clot dissolution.

17. Llevadot *et al.* teach that t-Pa administration can be used to treat myocardial infarction thrombosis.

18. It would have been obvious to the skilled artisan to administer the Factor Xaγ taught by Grundy *et al.* to subjects having thrombosis, satisfying claims 1, 3 and 10. The skilled artisan would have been motivated to do so in light of the teaching of Llevadot *et al.* that t-Pa can be used to treat thrombosis and the teaching of Grundy *et al.* that Factor Xaγ accelerates t-Pa. There

would have been a reasonable expectation of success given that Grundy *et al.* teach that Factor Xaγ leads to enhanced plasmin generation. With respect to claim 4, it would be obvious to administer the Factor Xaγ prophylactically because it is obvious to use Factor Xaγ therapeutically. With respect to claims 15 and 16, it would have been further obvious to administer both Factor Xaγ and heparin given that Llevadot *et al.* also teach that heparin can be used to treat thrombosis. With respect to claim 17, it is obvious to optimize the mode of administration through routine experimentation.

Response to Arguments Filed 11/20/2009

19. The arguments traversing the rejections under 35 U.S.C. 103(a) filed 11/20/2009 and the declaration under 37 CFR 1.132 have been fully considered and are not found to be persuasive.

20. Applicant traverses the rejection on the grounds that there is no reasonable expectation of success that Factor Xaγ could be used to treat thrombosis based on the teaching of Grundy, Gladstone and Llevadot. The declaration in paragraph 5 filed 11/20/2008 under 37 CFR 1.132 states that:

> In the art, it is known that binding assays (such as those presented in Grundy) are not a reliable predictor of coagulation protein function. In the context of tPA accelerators, the reason is that the accepted gold standard physiological tPA accelerator is the clot itself (i.e. fibrin). The clot is in vast excess over Factor Xaγ. Therefore, according to current art, the clot would logically overwhelm any effects of Factor Xaγ.

21. The Inventor is arguing that because the data presented in Grundy is from an *in vitro* solution assay conducted in the absence of fibrin, the skilled artisan could not be certain if the observed effect of tPA acceleration would occur *in vivo*, or if the fibrin, a known tPA accelerator

present at high concentration near tPA, would overwhelm the effect of Factor Xaγ. Applicant supports this position in paragraphs 8 and 9 of the declaration citing numerous examples of proteins that bind tPA but do not acclerate tPA *in vivo* or in the presence of fibrin. To further support the position that the skilled artisan would not be able to predict if Factor Xaγ could be successfully used to treat thrombosis based on the teaching of Grundy, Applicant presents comments from anonymous peer reviewers (i.e. skilled artisans) who reviewed the grant application that supported the work of the instant application (Appendix B) and a manuscript (Appendix C). Both reviewers question the clinical relevance of the observation that Factor Xaγ accelerates tPA in solution, consistent with Applicant's position (see Appendix B and C and page 7 of the arguments filed 11/20/2009).

22. Applicant's arguments are not persuasive because although the prior art does not teach with absolute certainty that Factor Xaγ could be used to treat thrombosis, there is a reasonable expectation of success and a degree of predictability associated with the outcome that was available to the skilled artisan at the time the invention was filed.

23. MPEP § 2105 states: "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)"

24. In the instant case, Applicant has attempted to provide evidence showing that there was no reasonable expectation of success. The evidence provided however suggests that although there is no absolute predictability associated with the use of Factor Xaγ to treat thrombosis, there is a degree of predictability. In Appendix B the anonymous grant reviewer states:

> Of concern, however, is that the observations were made in the absence of fibrin. The applicant must demonstrate that plasmin catalyzed cleavage of prothrombinase components enhance tPA-mediated fibrinolysis not just tpA-dependent activation of plasminogen in solution. This could be done with purified components or plasma depleted of various components....Positive results would indicate whether measurement of plasmin cleaved FX/Xa/V/Va products in plasma is relevant. If an effect is observed the concentration dependence of this effect will either substantiate or refute applicant's hypothesis that these components would be clinically advantageous. ...Subsequently, the applicant must demonstrate that' not only are the components produced during fibrinolysis but that they are produced in a time-course that would facilitate tPA-mediated fibrinolysis

This passage illustrates that the skilled artisan would, based on the observation that Factor Xaγ accelerates tPA in solution, formulate the hypothesis that Factor Xaγ may be clinically relevant and would test the hypothesis using defined, predictable experiments such as assays in plasma. The skilled artisan as represented by the grant reviewer would also know how to interpret the results of the experiments with respect to the clinical relevance of the Factor Xaγ. The additional experimentation required to validate the use of Factor Xaγ to treat thrombosis is within the skill of the art at the time.

25. Thus, the rejection of the claims under 35 U.S.C. 103(a) is maintained. Although Applicant's arguments were persuasive to show that there was no absolute certainty that Factor Xaγ would be successful to treat thrombosis, this level of certainty or predictability is not required. Based on the knowledge of the skilled artisan, as evidenced by Appendix B in the declaration filed 11/20/2008, there was predictability associated with the use of Factor Xaγ to treat thrombosis at the time the invention was filed.

Double Patenting

26. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

27. An amendment to the claims in copending Application 11/451,959 filed 02/04/2009 in which claims 1-12 were withdrawn necessitates the following new grounds of rejection. The previous rejection of claims 5, 6, 11 and 20-23 is moot because these claims were cancelled in the response filed 11/20/2008. The previous grounds of rejection was not traversed by Applicant in the response filed 11/20/2008.

28. Claims 1, 3, 4 10, and 15-17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29-36 of copending Application No. 11/451,959, in view of Grundy *et al.* (*Biochem.*, **2001**, *40*, 6293-6302, citation 1 on the Information Disclosure Statement filed 11/28/2007), Gladstone *et al.* (*CNAJ*, **2001**, *165*, 311-7) and Llevadot *et al.* (*JAMA*, **2001**, *286*, 442-9). Although the conflicting claims are not identical, they are not patentably distinct from each other.

29. Claim 31 of copending Application No. 11/451,959 is drawn to a pharmaceutical composition comprising a Factor X derivative selected from a 33 KD fragment of Factor Xa comprising a C-terminal lysine at a position selected from Lys330, Lys338, Lys351 and combinations thereof, a 13 KD fragment of Factor Xa comprising a C-terminal lysine residue at a position selected from Lys435, Lys333, Lys327 and combinations thereof, and a noncovalent heterodimer between the 33 and 13 KD fragments of Factor Xa

30. Claims 29-36 of copending Application No. 11/451,959 do not recite a method of administering this pharmaceutical composition to treat thrombosis.

31. Grundy *et al.* teach that PN cleavage of Factor Xa under phospholipid binding conditions yields three fragments, two of which are 33 and 13 kD (Figure 1). Grundy *et al.* also teach that these fragments have exposed C-terminal lysine residues, that they play a role in fibrinolysis (or blood clot dissolution) and that they accelerate tissue plasminogen activator (t-PA) resulting in enhanced plasmin generation (p. 6294, col. 1). Grundy *et al.* teach compositions comprising these fragments, Factor Xaγ33/13 (p. 6294, col. 1).

32. Gladstone *et al.* teach that t-Pa administration can be used to treat stroke thrombosis.

33. Llevadot *et al.* teach that t-Pa administration can be used to treat myocardial infarction thrombosis.

34. It would have been obvious to the skilled artisan to administer the Factor Xa derivative recited in claim 29 of copending Application 11/451,959 to subjects having thrombosis. The composition in claim 29 of the conflicting case meets the requirements for Factor Xaγ recited in page 7, lines 1-7 of the instant specification. The skilled artisan would have been motivated to do so based on the teaching of Grundy that Factor Xaγ33/13 play a role in fibrinolysis (or blood

clot dissolution) and that they accelerate tissue plasminogen activator (t-PA) resulting in enhanced plasmin generation (p. 6294, col. 1). The skilled artisan would have been further motivated to do so in light of the teaching of Gladstone *et al.* that t-Pa administration can be used to treat stroke thrombosis and Llevadot *et al.* that t-Pa can be used to treat myocardial infarction thrombosis. In other words, it would have been obvious to administer Factor Xaγ, a composition that accelerates a known treatment of thrombosis (i.e. t-Pa) to treat thrombosis. There would have been a reasonable expectation of success given that Grundy *et al.* teach that Factor Xaγ leads to enhanced plasmin generation. With respect to claim 4, it would be obvious to administer the Factor Xaγ prophylactically because it is obvious to use Factor Xaγ therapeutically. With respect to claims 15 and 16, it would have been further obvious to administer both Factor Xaγ and heparin given that Llevadot *et al.* also teach that heparin can be used to treat thrombosis. With respect to claim 17, it is obvious to optimize the mode of administration through routine experimentation.

35. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

36. No claims are allowed.

37. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

38. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 8:30 A.M. to 4:00 P.M.

39. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

40. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
Primary Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

cmb